AD_____

Award Number: W81XWH-08-1-0577

TITLE: Dietary and Environmental Exposure to Cadmium and the Risk of Breast Cancer

PRINCIPAL INVESTIGATOR: Dr. Rudolph Rull, Ph.D.

CONTRACTING ORGANIZATION: Cancer Prevention Institute of California
Fremont, CA 94538

REPORT DATE: October 2011

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
01-10-2011	Annual	15 SEP 2010 - 14 SEP 2011

4. TITLE AND SUBTITLE

Dietary and Environmental Exposure to Cadmium and the Risk of Breast Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-1-0577

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Dr. Rudolph Rull, Ph.D.

E-Mail: rudy.rull@cpic.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Cancer Prevention Institute of California
Fremont, CA 94538

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This proposed study will examine whether exposure to cadmium (Cd) from dietary or environmental sources increases the risk of breast cancer. We will examine this hypothesis using information collected from the California Teachers Study (CTS) cohort, a group of approximately 130,000 female school employees living in California followed for breast cancer since 1995. Information collected by questionnaire includes residential addresses, exposure to tobacco smoke, and food and beverage consumption. We will assess levels of dietary and environmental exposure by linking these collected data with available information on Cd residue levels in foods and beverages and environmental sources of Cd pollution near women's residences. In addition, we will estimate total Cd exposure by using existing urine samples provided by 304 women in the CTS to determine the relative contributions of dietary and environmental sources to the level of urinary Cd, which is considered a good measure of cumulative lifetime exposure. We will then evaluate whether dietary, environmental, and total exposure to Cd increase the risk of breast cancer.

We made substantial progress in the third year of the study. Using assessed dietary and environmental exposures for the entire CTS cohort, we conducted several analyses to evaluate whether Cd increases the risk of breast cancer. We observed an increased risk for ER- breast cancer associated with residential proximity to high vehicular traffic density and with residence in a census tract with an elevated Cd concentration in ambient air. We are nearing completing our first manuscript on measured urinary Cd concentrations obtained from the sub-study of 304 women. In addition, we are preparing manuscripts on the breast cancer risk analyses.

15. SUBJECT TERMS

Cadmium, diet, environment, breast cancer, biomarkers

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
U	U	U	UU	42	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

INTRODUCTION

This proposed study will examine whether exposure to cadmium (Cd) from dietary or environmental sources increases the risk of breast cancer. We will examine this hypothesis using information collected from the California Teachers Study (CTS) cohort, a group of approximately 130,000 female school employees living in California followed for breast cancer since 1995. Information collected by questionnaire includes residential addresses, exposure to tobacco smoke, and food and beverage consumption. We will assess levels of dietary and environmental exposure by linking these collected data with available information on Cd residue levels in foods and beverages and environmental sources of Cd pollution near women's residences. In addition, we will estimate total Cd exposure by using existing urine samples provided by 304 women in the CTS to determine the relative contributions of dietary and environmental sources to the level of urinary Cd, which is considered a good measure of cumulative lifetime exposure. We will then evaluate whether dietary, environmental, and total exposure to Cd increase the risk of breast cancer.

This annual report documents the progress made in the third year of the project. We received a no-cost extension for one year and expect to complete project activities in September 2012.

BODY

In the third year of this project, we made substantial progress on Tasks 6-9 listed in the Statement of Work. These tasks and their progress are documented in this section.

Task 6 (Months 20–24)**:** Evaluate the contribution from dietary and environmental sources to total Cd exposure based on urinary Cd concentrations.

a. Develop mixed-effects models.

b. Run these models with urinary Cd concentration as the dependent variable to calibrate exposures from dietary and environmental sources and other covariates in the validation sub-study population.

c. Conduct formal evaluation of effect modification with stratified models or models with interaction terms.

d. Evaluate model precision using iterative cross-validation.

Progress: We have completed this task and are finalizing a manuscript of these results.

Descriptive statistics for demographic factors, dietary and environmental Cd exposure estimates and measured urinary Cd levels of women participating in the exposure validation sub-study are provided in Table 1. Because the distribution of urinary Cd concentrations was skewed, we used a natural log transformation to normalize the distribution. The median age of participants in this study was 55 years old, the median body mass index was 25 kg/m^2, and most never smoked. Traffic density and industrial Cd emissions ranged over several orders of magnitude, while estimated dietary Cd intake and Cd concentrations in ambient air had 3 – 4 fold ranges among participants. The median values of urinary Cd concentration, creatinine-adjusted urinary Cd, concentration and 24-hour urinary Cd output were 0.3 μg/L, 0.4 μg/g, and 0.5 μg respectively for the first urine sample collected.

The intraclass correlation coefficient among participants with repeated measurements was 0.50 for urinary Cd concentration (Figure 1) and 0.42 for creatinine-adjusted urinary Cd concentration, indicating moderate correlation within a person over time. Among the 141 participants with two urine samples analyzed, the variance in urinary Cd levels was similar between and within persons. One implication of the modest correlation between repeat samples is that measurement error from using a single urinary Cd measure to estimate exposure in a case-control study would result in about a -50% bias of the estimated odds ratio towards the null.

Distributions from non-parametric univariate analyses of self-reported categorical characteristics and urinary Cd levels from the first urine sample (n=296) are shown in Table 2. There was a significant increase in urinary Cd concentration with age and the relationship was stronger for creatinine-adjusted concentrations ($p < 0.0001$). The mean urinary Cd concentration among current smokers was twice as high as the mean levels among former and never smokers. Participants who reported consuming more than 20 g (one drink) of alcohol per day had significantly lower urinary Cd concentrations than participants who did not drink alcohol. Increasing parity was also related to lower urinary Cd levels and the relationship was stronger for creatinine-adjusted urinary Cd ($p < 0.0002$). Larger body surface area was associated with lower urinary Cd concentrations, but not for creatinine-adjusted levels. The was no observed association between urinary Cd levels and body mass index, breast feeding history, oral contraceptive use or hormone replacement therapy. There was little difference between urinary Cd concentrations based on categories of estimated exposure to environmental sources (parameter estimates listed in Table 3). Urban residents had slightly higher urinary Cd concentrations than rural residents, and participants with the highest category of estimated exposure to industrial Cd emissions had slightly higher levels of urinary Cd than those with no Cd emissions within five kilometers of their residence, but neither of these differences was statistically significant.

Table 4 lists parameter estimates from the final multivariate linear mixed effects models of urinary Cd concentrations with smoking as a predictor variable (Model 1) and among never smokers with passive smoking intensity as a predictor variable (Model 2). The total variability explained by both models was similar (R^2 = 42–44%). Creatinine concentration (27%) and age (6–8%) explained the greatest variability in urinary Cd concentrations. Total pack-years of smoking in Model 1 and lifetime intensity of passive smoking in Model 2 were significant predictors. In both models, increasing parity, alcohol intake and body surface area were associated with lower urinary Cd concentrations. Dietary and environmental estimates of Cd exposure were not significant predictors of urinary Cd concentrations in this sample. Using iterative cross-validation where we reran the models using randomly-selected sets of 90% of subjects, we determined that the models were not over fit, with the same variables significant in each subset of the data, similar regression coefficients (~10%) and similar overall R^2 values (40 – 46%). In generalized estimating equation models with robust standard errors, we observed that the same explanatory variables were significant and the regression coefficients were very similar.

We are finalizing a manuscript of these findings. These findings were presented at the Era of Hope meeting in August 2011 in Orlando, Florida. As mentioned in the previous annual report, the positive associations of age and smoking with urinary Cd concentration have been previously demonstrated (Ikeda et al., 2005; McElroy et al., 2007). The lack of an observed association between estimated dietary intake of Cd and urinary concentration is consistent with previous studies in low-exposure populations (McElroy et al., 2007), but such an association has only been observed in populations consuming Cd-contaminated food (Ikeda et al., 2006; Yamagami et al., 2006). We observed a negative relationship between parity and Cd concentration, unlike a previous study (McElroy et al., 2007). An association between reduced body burden levels and number of pregnancies is consistent with other studies of persistent pollutants (Wolff et al., 2005; Verner et al., 2008). We also observed a negative association between urinary Cd concentrations and average daily alcohol consumption, which was observed in a previous study (McElroy et al., 2007). However, we did not observe a negative association between body size (body mass index or body surface area) and urinary Cd concentrations that was observed in previous studies (McElroy et al., 2007; Dhooge et al., 2010).

Task 7 (Months 24–26)**:** Generate estimates of total Cd exposure for all subjects in the CTS cohort.

a. Apply β's estimated from mixed-effects models as weights for the dietary and environmental exposure estimates for all subjects in the CTS.

b. Estimate total Cd exposure for all CTS subjects.

Progress: This task is complete.

Table 5 lists the distributions of demographic and personal characteristics of women enrolled in the CTS cohort. Table 6 lists the distributions of Cd exposure from environmental sources for all eligible CTS subjects, including from traffic density (vehicle kilometers traveled within 300 m), industrial Cd emissions (kg/km within 5 km), and estimated outdoor Cd concentration of the residential census tract (ng/m3). Table 7 lists the distributions of daily Cd dietary intake (μg/day) for all eligible CTS subjects. In addition to the unadjusted total, we also list the calorie-adjusted intake (adjusted for daily calories excluding alcohol ÷ 1,000) as well as the calorie-adjusted intake derived using the residual method. Because of the largely null associations between urinary Cd concentrations and estimated dietary and environmental Cd exposures, we did not have statistically significant parameter estimates from the mixed-effects models used in the exposure validation sub-study (Task 6) that would have served as weights for the dietary and environmental exposures to estimate total Cd exposure. As a result, our risk analyses will focus on dietary and environmental Cd exposures, but not total exposure.

Task 8 (Months 27–32)**:** Estimate the effects of total, dietary, and environmental exposure to Cd on breast cancer incidence in the CTS from 1996 to 2005.

a. Develop Cox proportional hazards models for estimating effects of exposure to Cd on breast cancer risk in the CTS.

b. Estimate hazard ratios for Cd exposure from specific sources and from all sources.

c. Conduct formal evaluation of effect modification.

Progress: We have mostly completed these analyses.

The following risk analyses of dietary exposure are based on calorie-adjusted dietary Cd intake estimated using the residual method. Effect estimates based on unadjusted and calorie-adjusted intake were similar to those derived based on residual-method-derived Cd intake. Because of the availability of ER+ and ER- status and a priori information that these breast cancer types have different etiologies, we conducted analyses stratified by ER-status.

Table 8 lists hazard ratios (HRs) and 95% confidence intervals (CIs) for ER+ breast cancer and quintiles of daily dietary Cd intake. The first column is adjusted only for total daily calories. Here, we observe an increased risk associated with dietary Cd, where the rate is 16% higher (95% CI: 2−33%) in the highest quintile compared with the lowest quintile (p-trend = 0.01). The second column presents HRs from a model adjusted for total daily calories and the following confounding variables: parity (no, yes) and age at first full term pregnancy (continuous), history of benign breast disease (no, yes), family history of breast cancer (no, yes, adopted), alcohol consumption in the year prior to baseline (none, <20 g/d, 20+ g/d), menopausal status and HT use at baseline (premenopausal, peri-/post-menopausal: never HT, current E+P, current E alone, past HT), BMI at baseline (continuous), height at baseline (continuous), and smoking status (never, former, current). In this model, we observed slightly lower HRs compared with the calorie-only-adjusted model but still observed an increase in rates consistent with a monotonic exposure-response pattern (p-trend = 0.03).

However, we were concerned that dietary patterns may additionally confound the observed trend. In a previous analysis, we identified five dietary patterns in the CTS cohort using principal components analysis: plant-based, high-protein/high-fat, high-carbohydrate, ethnic, and salad-and-wine (Chang et al., 2008). Evaluating each of these dietary patterns as potential confounders of the dietary Cd and ER+ breast cancer association, only the salad-and-wine dietary pattern appeared to significantly change the magnitude of the effect estimates. The third column of Table 8 lists HRs for quintiles of dietary Cd, adjusted for all previously listed covariates and the salad-and-wine dietary pattern. These HRs suggest that there is no association between dietary Cd (p-trend = 0.48). This result is not surprising, given the fact that while leafy green vegetables are an important dietary source of Cd, they are also rich in antioxidants and other beneficial nutrients. Consequently, a true adverse effect of dietary Cd on risk may be offset by the beneficial effects of other nutrients, thus leading to the observed null result when adjusting for the salad-and-wine dietary pattern.

We evaluated whether the salad-and-wine dietary pattern modified the effect of dietary Cd on ER+ breast cancer risk by comparing levels of these two exposures to a common reference group of women with low dietary Cd intake (< 8.23 μg/day) and a low salad-and-wine dietary pattern score (< 25th percentile). Table 9 lists HRs by level of these two exposures. By level of salad-and-wine dietary pattern, we observed elevated risk in the medium (25th–<75th percentile) and high (≥ 75th percentile). However, HRs for dietary Cd intake within the medium and high levels of salad-and-wine dietary pattern did not appear to differ with one another. Thus, we did not see any evidence of an interaction. We are currently evaluating whether it is possible to evaluate whether Cd intake from foods other than leafy green vegetables increases the risk of ER+ breast cancer.

Table 10 lists HRs and 95% confidence intervals (CIs) for ER- breast cancer and quintiles of daily dietary Cd intake. The first column is adjusted only for total daily calories. Here, we observe a negative association between dietary Cd and risk, where the rate is 70% (95% CI: 51−96%) the rate in the in the highest quintile compared with the lowest quintile (p-trend = 0.05). The second column presents HRs from a model adjusted for total daily calories and the following confounding variables: birthplace (North American born, not North American born), age at menarche (continuous from ≤9 to 17+), history of benign breast disease (no, yes), family history of breast cancer (no, yes, adopted), average lifetime (high school to age 54) moderate physical activity (hours per week; continuous), alcohol consumption in the year prior to baseline (none, any), menopausal status and hormone therapy use at baseline (premenopausal, peri-/post-menopausal: never hormone therapy, ever hormone therapy), BMI at baseline (continuous), and continuous factor scores for the following dietary factors in the year prior to baseline: "high protein and high fat", "high carbohydrate", and "ethnic". HRs in this model were similar to those observed in the minimally-adjusted model. However, additional adjustment for antioxidant intake from vegetables (ORAC_OH) reduced the magnitude of the observed exposure-response pattern (p-trend = 0.36).

Similar to the joint analysis of dietary Cd and the salad-and-wine dietary pattern for the risk of ER+ breast cancer, we evaluated the joint effect of dietary Cd and antioxidants from vegetables on the risk of ER- breast cancer using a common reference group of women in the lowest tertiles of low dietary Cd intake and antioxidant (ORAC_OH) score (Table 11). By tertile of level of antioxidant score, we observed reduced risks in the higher tertiles. However, HRs for dietary Cd intake within the medium and high levels of antioxidants did not appear to differ with one another, suggesting no interaction. Similar to observation about the dietary Cd and the salad-and-wine dietary pattern for ER+ breast cancer, the fact that Cd and antioxidants both come from leafy green vegetables contributes to the challenge of identifying the independent effect of Cd intake.

We are currently completing stratified analyses of dietary intake and breast cancer risk by subtype and are developing a manuscript.

Tables 12-14 lists effect estimates for all invasive breast cancers and Cd exposures from multiple environmental sources: vehicular traffic density (vehicle km traveled within 300m; Table 12), industrial Cd emissions (kg/km within 5 km; Table 13), and estimated outdoor Cd concentrations (census-tract level, Table 14). In these initial analyses, we estimated effects in the entire CTS cohort and three sub-populations: women resided in the same residential address since baseline (non-movers), women who reported never smoking in their lifetime (never smokers), and non-moving never-smoking women.

Models in these tables were first minimally adjusted for age and race/ethnicity, and then for the following additional variables: family history of breast cancer, age at menarche, pregnancy history, breast feeding history, physical activity, alcohol consumption, BMI, menopausal status/hormone therapy combined, smoking status, smoking pack-years, home environmental tobacco smoke exposure. For quartiles of traffic density (Table 12) and categories of proximity to Cd emissions facilities (Table 13), we did not observe any associations with breast cancer risk. For categories and natural-log transformed estimated outdoor Cd concentrations (Table 14), we did not observe any associations with breast cancer risk.

Stratifying by ER+ and ER- breast cancer subtypes, we observed positive associations for the risk of ER- cancer and outdoor Cd concentrations (Table 15) and traffic density (Table 16), particularly among women who never smoked and never moved. For log-continuous outdoor Cd concentration (Table 15), we observed a HR of 1.24 (95% CI: 1.00−1.53) for ER- breast cancer among non-moving never-smoking women. Comparing the ≥90th percentile category with the <25th percentile category of exposure in this same sub-population, the HR was 1.24 (95% CI: 1.00−1.53). We observed similar patterns for the entire CTS cohort and the other sub-populations of women who never smoked and women who did not move, but the effect estimates were not statistically significant. In contrast, we did not observed any associations between ER+ breast cancer risk and outdoor Cd concentrations.

For quartiles of traffic density (Table 16), we observed elevated HRs associated with ER- breast cancer among non-moving never-smoking women. The HR for the highest quartile of exposure was 1.42 (95% CI: 0.97-2.07). No association was observed between traffic density and ER+ breast cancer.

We will conduct additional analyses of these environmental exposures, especially within strata of body mass index, menopausal status, and parity. We are actively preparing a manuscript on the effects of Cd exposures from environmental sources on ER- and other breast cancer subtypes.

Task 9 (Months 33–36)**:** Prepare final reports, finalize manuscripts and present findings.

a. Discuss and interpret study findings and their implications.

b. Prepare final reports.

c. Write manuscripts.

d. Present findings at scientific meetings.

Progress: We are currently writing our first manuscript on the comparison of urinary Cd concentrations with dietary and environmental Cd exposures in the exposure validation sub-study. In addition, we are preparing manuscripts on the effects of dietary Cd intake and environmental Cd exposures on breast cancer risk, especially within subtypes of this disease. We plan to present findings from this study at the International Society for Environmental Epidemiology conference in August 2012 in Columbia, South Carolina.

KEY RESEARCH ACCOMPLISHMENTS, YEAR 3

- Completion of assessments of environmental Cd exposure and dietary Cd intake in the CTS cohort.
- Creation of the analytic dataset for the evaluation of breast cancer risk.
- Identification of predictors of urinary Cd concentrations in the exposure validation sub-study.
- Presentation of study findings on the predictors of urinary Cd concentrations at Era of Hope meeting (see below).
- Completion of initial analyses of the effects of Cd from dietary intake and environmental exposures on breast cancer risk.

REPORTABLE OUTCOMES

We presented a poster of our findings from Tasks 3-6 at the Era of Hope meeting in Orlando, Florida in August 2011. The poster, titled "Urinary Cadmium Concentrations among Female Teachers from Northern California", described the results from our mixed-effects models (see Appendix 1 for abstract).

In August 2011, we received a grant from the California Breast Cancer Research Program to examine whether urinary Cd concentration is associated with early age at menarche and pubertal development in girls (see Appendix 2 for project summary/abstract). Similar to our study of Cd and endometrial cancer that was funded by the National Institutes of Health (Grant No. 1R01ES018841), this study was motivated by this study of Cd and breast cancer. In addition, it was motivated by the recent discovery of high levels of Cd in children's jewelry and toys (Becker et al., 2010).

CONCLUSION

We made substantial progress on all of the tasks scheduled for completion in the second year of this study and have already initiated the first manuscript of our study results. The completion of the assessment of dietary intake and environmental exposure and the analyses estimating the effects of these exposures on the risk of breast cancer in the third year of the study will contribute to the growing body of evidence regarding the carcinogenicity of Cd.

REFERENCES

Akesson, A. , Julin, B. , Wolk, A. Long-term dietary cadmium intake and postmenopausal endometrial cancer incidence: a population-based prospective cohort study. Cancer Res, 2008, 68:6435-41.

Barr, D. B. , Wilder, L. C. , Caudill, S. P. , Gonzalez, A. J. , Needham, L. L. , Pirkle, J. L. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. Environ Health Perspect, 2005, 113:192-200.

Becker, M. , Edwards, S. , Massey, R. I. Toxic chemicals in toys and children's products: limitations of current responses and recommendations for government and industry. Environ Sci Tech, 2010, 44:7986-91.

Chang, E. T. , Lee, V. S. , Canchola, A. J. , Dalvi, T. B. , Clarke, C. A., Reynolds, P. , Purdie, D. M. , et al. Dietary patterns and risk of ovarian cancer in the California Teachers Study cohort. Nutr Cancer, 2008, 60:285-91.

Dhooge, W. , Den Hond, E. , Koppen, G. , Bruckers, L. , Nelen, V. , Van De Mieroop, E. , Bilau, M. , Croes, K. , Baeyens, W. , Schoeters, G. , Van Larebeke, N. Internal exposure to pollutants and body size in Flemish adolescents and adults: associations and dose-response relationships. Environ Int, 2010, 36:330-7.

Ikeda, M. , Moriguchi, J. , Ezaki, T. , Fukui, Y. , Ukai, H. , Okamoto, S. , Shimbo, S. , Sakurai, H. Smoking-induced increase in urinary cadmium levels among Japanese women. Int Arch Occup Environ Health, 2005, 78:533-40.

Ikeda M. , Shimbo S. , Watanabe T. , Yamagami T. Correlation among cadmium levels in river sediment, in rice, in daily foods and in urine of residents in 11 prefectures in Japan. Int Arch Occup Environ Health. 2006, 79:365-70.

McElroy, J. A. , Shafer, M. M. , Hampton, J. M. , Newcomb, P. A. Predictors of urinary cadmium levels in adult females. Sci Total Environ, 2007, 382:214-23.

Verner M. A. , Charbonneau M. , López-Carrillo L. , Haddad S. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: a new tool in breast cancer epidemiologic studies. Environ Health Perspect, 2008, 116:886-92.

Wolff M. S. , Deych E. , Ojo F. , Berkowitz G. S. Predictors of organochlorines in New York City pregnant women, 1998-2001. Environ Res, 2005, 97:170-7.

Yamagami, T. , Ezaki, T. , Moriguchi, J. , Fukui, Y. , Okamoto, S. , Ukai, H. , Sakurai, H. , Aoshima, K. , Ikeda, M. Low-level cadmium exposure in Toyama City and its surroundings in Toyama prefecture, Japan, with references to possible contribution of shellfish intake to increase urinary cadmium levels. Sci Total Environ, 2006, 362:56-67.

SUPPORTING DATA

Table 1. Distributions of demographic, geographic and laboratory characteristics (CTS exposure validation sub-study, N = 296).

Table 2. Distributions of self-reported categorical characteristics and cadmium concentrations from initial visit, unadjusted and adjusted for creatinine (CTS exposure validation sub-study, N = 296).

Table 3. Comparisons of environmental categorical characteristics and cadmium concentrations from initial visit unadjusted and adjusted for creatinine (CTS exposure validation sub-study, N = 296).

Table 4. Results from multilevel linear regression models for the natural logarithm of cadmium concentration (μg/L) (CTS exposure validation sub-study).

Table 5. Characteristics among women with no prior history of breast cancer through 2007 and who resided in California at the time of the baseline questionnaire (California Teachers Study cohort, N = 114,253).

Table 6. Distributions of environmental Cd exposures from environmental sources among women with no prior history of breast cancer through 2007 and who resided in California at the time of the baseline questionnaire (California Teachers Study cohort, N = 114,253).

Table 7. Distributions of daily dietary Cd intake among women with no prior history of breast cancer through 2007 who resided in California at the time of the baseline questionnaire with complete dietary data (California Teachers Study cohort).

Table 8. Hazard ratios and 95% confidence intervals for ER+ breast cancer (n = 2,385) and quintiles of calorie-adjusted dietary Cd intake[a], California Teachers Study cohort (N = 85,509).

Table 9. Hazard ratios and 95% confidence intervals for ER+ breast cancer (n = 2,385) by tertile of calorie-adjusted dietary Cd intake[a] and tertile of intake from vegetables (ORAC_OH, calorie-adjusted using the residual method, continuous) using a common reference category, California Teachers Study cohort (N = 85,509).

Table 10. Hazard ratios and 95% confidence intervals for ER− breast cancer (n = 409) and quintiles of calorie-adjusted dietary Cd intake[a], California Teachers Study cohort (N = 84,865).

Table 11. Hazard ratios and 95% confidence intervals for ER− breast cancer (n = 409) by tertile of calorie-adjusted dietary Cd intake[a] and tertile of antioxidant intake from vegetables using a common reference category, California Teachers Study cohort (N = 84,865).

Table 12. Hazard ratios and 95% confidence intervals for breast cancer and vehicular traffic density (vehicle km traveled within 300m), by quartile categories, California Teachers Study cohort.

Table 13. Hazard ratios and 95% confidence intervals for breast cancer and industrial Cd emissions (kg/km within 5 km), by categories of exposure, California Teachers Study cohort.

Table 14. Hazard ratios and 95% confidence intervals for breast cancer and estimated outdoor cadmium concentration, by categories of exposure and natural-logarithmic continuous exposure, California Teachers Study cohort.

Table 15. Hazard ratios and 95% confidence intervals for ER-positive and ER-negative breast cancer and estimated outdoor cadmium concentration, by categories of exposure and natural-logarithmic continuous exposure, California Teachers Study cohort.

Table 16. Hazard ratios and 95% confidence intervals for ER-positive and ER-negative breast cancer and traffic density (vehicle km traveled within 300m), by quartile categories, California Teachers Study cohort.

Figure 1. Intraclass correlation for repeated measurements of cadmium in urine (CTS exposure validation sub-study, n=141).

Table 1. Distributions of demographic, geographic and laboratory characteristics (CTS exposure validation sub-study, N = 296).

Variable	Units	Number	25th percentile	50th percentile	75th percentile	Maximum	Mean	Standard deviation
Self-reported questionnaire and interview data								
Age	years	296	47	54	62	84	55	12
Body mass index	kg/m^2	293	23	25	29	61	27	5.9
Full-term births	number	291	0	2	3	6	1.7	1.4
Total pack-years smoked	pack years	296	0	0	1	61	3.9	10
Dietary Cd intake	µg/day	287	6.7	8.8	11	21	9.1	3.5
Geographic based exposure estimates								
Industrial emissions	kg/km within 5km	296	0	0	0.001	381	4.7	31
Ambient air concentration	ng/m^3	296	0.09	0.15	0.28	0.65	0.20	0.13
Traffic density	Vehicle km traveled within 300m	296	0	845	7,276	97,320	6,199	12,542
Laboratory results								
Cd concentration	µg/L	296	0.2	0.3	0.4	3.6	0.3	0.2
Creatinine concentration	g/L	296	0.5	0.7	1.0	2.5	0.8	0.4
Creatinine-adjusted Cd concentration	µg/g	296	0.3	0.4	0.5	1.5	0.4	0.2
Cd 24-hour output	µg	295	0.3	0.5	0.7	2.6	0.5	0.3

Table 2. Distributions of self-reported categorical characteristics and cadmium concentrations from initial visit, unadjusted and adjusted for creatinine (CTS exposure validation sub-study, N = 296).

Characteristic	n	%	Mean unadjusted Cd (μg/L)	Kruskal-Wallis p	p-trend[a]	Mean creatinine-adjusted Cd (μg/g)	Kruskal-Wallis p	p-trend[a]
Age (years)								
31 – 39	30	10%	0.30	0.11	0.01	0.32	<0.0001	<0.0001
40 – 49	63	21%	0.31			0.36		
50 – 59	114	39%	0.33			0.44		
60 – 84	89	30%	0.36			0.52		
Smoking								
Never	200	68%	0.31	0.01	0.01	0.40	0.001	0.002
Former	85	29%	0.33			0.49		
Current	10	3%	0.65			0.62		
Exposure to second-hand smoke (severity index)[b]								
< 4	39	24%	0.35	0.37	0.61	0.39	0.77	0.41
4 – 20	43	26%	0.36			0.46		
21 – 38	41	25%	0.30			0.38		
> 38	42	25%	0.32			0.42		
Alcohol (g/day)								
None	96	32%	0.40	0.0005	0.0001	0.50	0.0006	0.0001
< 20	174	59%	0.31			0.41		
> 20	26	9%	0.23			0.35		
Parity								
0	75	26%	0.33	0.65	0.02	0.46	0.39	0.0002
1 – 2	143	49%	0.31			0.43		
3	43	15%	0.34			0.42		
> 3	30	10%	0.30			0.41		
Time breastfeeding (months)								
≤ 1	81	27%	0.34	0.37	0.17	0.46	0.03	0.05
2 – 3	81	27%	0.35			0.46		
4 – 5	87	29%	0.32			0.38		
> 5	47	16%	0.30			0.44		

Body mass index (kg/m^2)								
< 22.7	78	26%	0.34	0.38	0.43	0.44	0.19	0.24
22.7 – 25.1	72	24%	0.35			0.48		
25.2 – 29.1	73	25%	0.29			0.41		
> 29.1	73	25%	0.35			0.41		
Body surface area (cm^2)								
< 1.65	73	25%	0.38	0.04	0.03	0.48	0.08	0.29
≥ 1.65	223	75%	0.31			0.42		
Dietary Cd intake (μg/day)								
< 7.62	72	25%	0.38	0.66	0.10	0.46	0.69	0.54
7.62 – 9.94	73	25%	0.31			0.43		
9.95 – 12.73	72	25%	0.32			0.41		
> 12.73	74	25%	0.30			0.44		

[a] Linear test for trend with natural logarithm transformed concentrations adjusted for age.

[b] Among never smokers that answered questionnaire about exposure to second-hand smoke (n=165).

Table 3. Comparisons of environmental categorical characteristics and cadmium concentrations from initial visit unadjusted and adjusted for creatinine (CTS exposure validation sub-study, N = 296).

Characteristic	n	%	Mean unadjusted Cd (μg/L)	Kruskal-Wallis p	p-trend	Mean creatinine-adjusted Cd (μg/g)	Kruskal-Wallis p	p-trend
Urban or rural residence								
Urban	119	40%	0.35	0.12	0.17	0.45	0.08	0.42
Rural	177	60%	0.32			0.42		
Estimated outdoor cadmium concentration (ng/m^3)								
< 0.1	94	32%	0.31	0.37	0.29	0.42	0.34	0.31
0.1 – 0.3	142	48%	0.34			0.44		
> 0.3	60	20%	0.34			0.43		
Traffic density (vehicle kilometers traveled within 300 m)								
0	101	34%	0.33	0.78	0.82	0.43	0.64	0.54
1 – 7,000	48	16%	0.35			0.42		
7,001 – 70,000	118	40%	0.32			0.43		
> 70,000	29	10%	0.33			0.46		
Industrial Cd emissions (kg/km within 5 km)								
0	203	69%	0.33	0.23	0.06	0.43	0.57	0.23
0.01 – 20	52	18%	0.33			0.42		
> 20	41	14%	0.35			0.45		

Table 4. Results from multilevel linear regression models for the natural logarithm of cadmium concentration (μg/L) (CTS exposure validation sub-study).

	Model 1: all subjects, pack-years smoking included as a predictor		Model 2: non-smokers, passive smoking history included as a predictor	
Number of subjects (samples)	287 (422)		164 (239)	
Variable	β (95% CI)	p (R^2)	β (95% CI)	p (R^2)
Intercept	-2.1 (-2.3, -1.8)		-2.0 (-2.4, -1.7)	
Creatinine (g/L)	0.93 (0.30, 1.06)	<0.001 (0.27)	0.89 (0.73, 1.05)	<0.001 (0.27)
Age (centered to age-31 years)	0.014 (0.009, 0.019)	<0.001 (0.35)	0.011 (0.0036)	0.004 (0.33)
Total pack-years smoking	0.010 (0.005, 0.016)	<0.001 (0.37)	–	
Total lifetime intensity of passive smoking	–		0.002 (0.00009, 0.004)	0.04 (0.37)
Total births	-0.047 (-0.09, -0.005)	0.03 (0.39)	-0.04 (-0.09, 0.01)	0.14 (0.39)
Alcohol intake	-0.17 (-0.26, -0.077)	<0.001 (0.40)	-0.17 (-0.28, -0.05)	0.005 (0.40)
Body surface area (2 categories)	-0.14 (-0.26, -0.014)	0.03 (0.41)	-0.16 (-0.32, 0.003)	0.06 (0.42)
Estimated cadmium concentration in air (3 categories)	-0.012 (-0.13, 0.10)	0.84 (0.41)	0.10 (-0.05, 0.25)	0.18 (0.43)
Industrial emissions within 5 km (3 categories)	0.053 (-0.051, 0.16)	0.32 (0.41)	0.041 (-0.10, 0.18)	0.57 (0.43)
Traffic density within 300m (4 categories)	-0.050 (-0.11, 0.01)	0.11 (0.41)	-0.058 (-0.14, 0.019)	0.14 (0.43)
Dietary cadmium intake (4 categories)	-0.011 (-0.057, 0.035)	0.65 (0.42)	-0.034 (-0.094, 0.026)	0.27 (0.44)

Table 5. Characteristics among women with no prior history of breast cancer through 2007 and who resided in California at the time of the baseline questionnaire (California Teachers Study cohort, N = 114,253).

Characteristic	Case (n=4,419)	Non-case (n=109,834)	Total (n=114,253)
	%	%	%
Race			
White	89.0	86.1	86.2
Black	2.6	2.7	2.7
Hispanic	2.7	4.4	4.4
Asian/PI	3.3	3.7	3.7
Other	2.4	3.1	3.0
Age (years) (mean (SD))	58.2 (11.8)	52.6 (14.5)	52.8 (14.5)
Family history of BC			
Yes	17.5	11.5	11.7
No	79.0	84.7	84.5
Unknown	3.5	3.8	3.8
Age at menarche (years)			
≤11	23.4	22.1	22.1
12-13	55.4	55.9	55.9
≥14	19.8	20.4	20.4
Unknown	1.4	1.6	1.6
Age at first full-term pregnancy (years)			
Nulliparous	22.7	26.5	26.3
<25	27.8	25.5	25.6
25-29	30.8	29.1	29.2
≥30	16.9	16.9	16.9
Unknown	1.8	2.0	2.0
Breast feeding history (months)			
Nulliparous	17.8	20.5	20.4
Pregnant without a live birth	4.8	5.9	5.8
None	19.7	15.9	16.1
< 6	18.3	17.6	17.5
6-11	14.0	13.5	13.5
≥12	23.2	24.3	24.3
Unknown	2.2	2.5	2.4

Physical activity (hours/week)			
0.00-0.50	36.2	29.8	30.0
0.51-2.00	31.7	31.8	31.8
2.01-3.50	15.0	17.5	17.4
3.51-5.00	8.5	9.5	9.5
>5.00	7.6	10.6	10.5
Unknown	1.0	0.7	0.8
Alcohol consumption (g/day)			
None	29.1	32.1	32.0
<20	55.0	54.8	54.8
≥20	11.0	7.6	7.7
Unknown	4.9	5.5	5.5
BMI (kg/m^2)			
16.0-24.9	55.1	58.7	58.5
25.0-29.9	27.0	23.5	23.7
≥30.0	13.5	13.4	13.4
Unknown/outlier	4.4	4.4	4.4
Menopausal status & HT use			
Pre-menopausal	22.2	41.2	40.5
Peri/post-menopausal & no HT use	12.4	11.8	11.8
Peri/post-menopausal & past HT use	7.5	6.8	6.9
Peri/post-menopausal & current HT use	42.5	26.8	27.4
Other/unknown	15.4	13.4	13.4
Smoking status			
Never	57.9	66.5	66.2
Former	34.7	27.9	28.1
Current	6.5	5.0	5.1
Unknown	0.9	0.6	0.6
Among former/current smokers:			
Total pack-years of smoking (mean (SD))	17.9 (18.7)	15.0 (17.6)	15.1 (17.6)
Average number of cigarettes smoked per day (mean (SD))	13.7 (10.5)	12.5 (10.2)	12.6 (10.3)
Among former smokers:			
Total years since quit smoking (mean (SD))	20.4 (11.3)	19.3 (11.5)	19.4 (11.5)
ETS residential exposure			
None	15.1	19.5	19.3

Childhood only	24.2	26.9	26.8
Adulthood only	18.7	16.8	16.9
Both childhood and adulthood	35.6	31.2	31.4
Unknown	6.4	5.6	5.6

Table 6. Distributions of environmental Cd exposures from environmental sources among women with no prior history of breast cancer through 2007 and who resided in California at the time of the baseline questionnaire (California Teachers Study cohort, N = 114,253).

Exposure	Cases	Non-cases	Total
Traffic density (vehicle kilometers traveled within 300 m)			
N	4,395	109,305	113,700
Mean (SD)	2,587 (4,618)	2,516 (4,465)	2,519 (4,471)
25th percentile	225	227	227
Median	1,207	1,172	1,174
75th percentile	3,062	2,997	2,999
Industrial Cd emissions (kg/km within 5 km)			
N	4,419	109,834	114,253
Mean (SD)	4.89 (54.74)	4.66 (95.54)	4.67 (94.29)
25th percentile	0.00	0.00	0.00
Median	0.00	0.00	0.00
75th percentile	0.11	0.13	0.13
Estimated outdoor cadmium concentration (ng/m^3)			
N	4,419	109,832	114,251
Mean (SD)	0.26 (0.31)	0.27 (0.32)	0.27 (0.32)
25th percentile	0.16	0.15	0.15
Median	0.21	0.21	0.21
75th percentile	0.28	0.29	0.29
Estimated outdoor cadmium concentration (natural log-transformed, ng/m^3)			
N	4,419	109,832	114,251
Mean (SD)	-1.53 (0.55)	-1.54 (0.57)	-1.54 (0.57)
25th percentile	-1.86	-1.87	-1.86
Median	-1.58	-1.57	-1.57

Table 7. Distributions of daily dietary Cd intake among women with no prior history of breast cancer through 2007 who resided in California at the time of the baseline questionnaire with complete dietary data (California Teachers Study cohort).

Daily dietary Cd intake	N	Mean	Standard Deviation	Minimum	25th percentile	Median	75th percentile	Maximum
Unadjusted	105,682	10.36	4.52	0.40	7.16	9.67	12.72	49.17
Calorie-adjusted (adjusted for daily calories excluding alcohol ÷ 1,000)	105,682	6.99	2.49	0.62	5.29	6.54	8.19	36.36
Calorie-adjusted using the residual method	105,682	9.96	3.41	0.85	7.62	9.40	11.66	47.13

Table 8. Hazard ratios and 95% confidence intervals for ER+ breast cancer (n = 2,385) and quintiles of calorie-adjusted dietary Cd intake[a], California Teachers Study cohort (N = 85,509).

			Minimally adjusted[b]			Fully adjusted[c]			Fully adjusted + salad & wine dietary pattern[d]		
Dietary Cd[a]	Cases	Person-years	HR[e]	95% CI	p-trend	HR[e]	95% CI	p-trend	HR[e]	95% CI	p-trend
<7.24	364	189,210	1.0			1.0			1.0		
7.24-8.69	395	187,954	1.00	0.86-1.15		0.98	0.85-1.13		0.96	0.83-1.10	
8.70-10.16	481	187,650	1.08	0.94-1.24		1.05	0.92-1.21		1.02	0.88-1.17	
10.17-12.32	537	185,803	1.12	0.98-1.28		1.09	0.95-1.25		1.03	0.90-1.19	
≥12.33	608	182,144	1.16	1.02-1.33	0.01	1.12	0.98-1.28	0.03	1.03	0.89-1.19	0.48

[a] Calorie adjusted using the residual method based on calories excluding alcohol.

[b] Adjusted for total calories (continuous).

[c] Additionally adjusted for parity (no, yes) and age at first full term pregnancy (continuous), history of benign breast disease (no, yes), family history of breast cancer (no, yes, adopted), alcohol consumption in the year prior to baseline (none, <20 g/d, 20+ g/d), menopausal status and HT use at baseline (premenopausal, peri-/post-menopausal: never HT, current E+P, current E alone, past HT), BMI at baseline (continuous), height at baseline (continuous) and smoking status (never, former, current).

[d] Additionally adjusted for a factor score measuring consumption of a 'salad and wine' dietary pattern in the year prior to baseline (continuous).

[e] Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Table 9. Hazard ratios and 95% confidence intervals for ER+ breast cancer (n = 2,385) by tertile of calorie-adjusted dietary Cd intake[a] and tertile of intake from vegetables (ORAC_OH, calorie-adjusted using the residual method, continuous) using a common reference category, California Teachers Study cohort (N = 85,509).

	Salad-and-wine dietary pattern								
Dietary Cd[a]	Low (<25th percentile)			Med (25th-<75th percentile)			High (≥75th percentile)		
(tertiles)	Cases	HR[b]	95% CI	Cases	HR[b]	95% CI	Cases	HR[b]	95% CI
<8.23	204	1.00	reference	342	1.12	0.94-1.33	83	1.17	0.90-1.53
8.23-10.76	121	1.06	0.85-1.33	437	1.12	0.94-1.33	230	1.21	0.99-1.48
≥10.77	58	0.98	0.73-1.31	398	1.16	0.98-1.38	512	1.28	1.08-1.53

[a] Calorie-adjusted using the residual method based on calories excluding alcohol.
[b] Adjusted for total calories (continuous), parity (no, yes) and age at first full term pregnancy (continuous), history of benign breast disease (no, yes), family history of breast cancer (no, yes, adopted), alcohol consumption in the year prior to baseline (none, <20 g/d, 20+ g/d), menopausal status and HT use at baseline (premenopausal, peri-/post-menopausal: never HT, current E+P, current E alone, past HT), BMI at baseline (continuous), height at baseline (continuous) and smoking status (never, former, current). HRs estimated using Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Table 10. Hazard ratios and 95% confidence intervals for ER− breast cancer (n = 409) and quintiles of calorie-adjusted dietary Cd intake[a], California Teachers Study cohort (N = 84,865).

			Minimally adjusted[b]			Fully adjusted[c]			Fully adjusted + antioxidants from vegetables[d]		
Dietary Cd[a]	Cases	Person-years	HR[e]	95% CI	p-trend	HR[e]	95% CI	p-trend	HR[e]	95% CI	p-trend
<7.24	84	188,112	1.0			1.0			1.0		
7.24-8.69	74	186,684	0.81	0.60-1.11		0.79	0.58-1.09		0.82	0.59-1.12	
8.70-10.16	80	186,488	0.78	0.58-1.07		0.76	0.56-1.05		0.81	0.58-1.11	
10.17-12.32	88	184,402	0.80	0.59-1.09		0.79	0.58-1.07		0.86	0.61-1.20	
≥12.33	83	180,381	0.70	0.51-0.96	0.05	0.69	0.50-0.95	0.05	0.79	0.53-1.16	0.36

[a] Calorie-adjusted using the residual method based on calories excluding alcohol.
[b] Adjusted for total calories (continuous).
[c] Additionally adjusted for birthplace (North American born, not North American born), age at menarche (continuous from ≤9 to 17+), history of benign breast disease (no, yes), family history of breast cancer (no, yes, adopted), average lifetime (high school to age 54) moderate physical activity (hours per week; continuous), alcohol consumption in the year prior to baseline (none, any), menopausal status and hormone therapy use at baseline (premenopausal, peri-/post-menopausal: never hormone therapy, ever hormone therapy), BMI at baseline (continuous), a factor score measuring consumption of a 'high protein and high fat' dietary pattern in the year prior to baseline (continuous), a factor score measuring consumption of a 'high carbohydrate' dietary pattern in the year prior to baseline (continuous) and a factor score measuring consumption of an 'ethnic' dietary pattern in the year prior to baseline (continuous).
[d] Additionally adjusted for antioxidant intake from vegetables (ORAC_OH, calorie-adjusted using the residual method, continuous) and its interaction with BMI and menopausal status/hormone therapy.
[e] Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Table 11. Hazard ratios and 95% confidence intervals for ER− breast cancer (n = 409) by tertile of calorie-adjusted dietary Cd intake[a] and tertile of antioxidant intake from vegetables using a common reference category, California Teachers Study cohort (N = 84,865).

Dietary Cd[a] (tertiles)	Tertiles of antioxidants from vegetables (ORAC_OH)								
	<2.12			2.12-2.88			≥2.89		
	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
<8.23	89	1.00	reference	37	0.87	0.59-1.28	7	0.57	0.26-1.25
8.23-10.76	37	0.78	0.53-1.14	68	0.89	0.65-1.23	35	0.73	0.49-1.10
≥10.77	11	0.92	0.49-1.74	44	0.76	0.53-1.11	81	0.65	0.47-0.89

[a] Calorie-adjusted using the residual method based on calories excluding alcohol.
[b] Adjusted for total calories (continuous), birthplace (North American born, not North American born), age at menarche (continuous from ≤9 to 17+), history of benign breast disease (no, yes), family history of breast cancer (no, yes, adopted), average lifetime (high school to age 54) moderate physical activity (hours per week; continuous), alcohol consumption in the year prior to baseline (none, any), menopausal status and hormone therapy use at baseline (premenopausal, peri-/post-menopausal: never hormone therapy, ever hormone therapy), BMI at baseline (continuous), a factor score measuring consumption of a 'high protein and high fat' dietary pattern in the year prior to baseline (continuous), a factor score measuring consumption of a 'high carbohydrate' dietary pattern in the year prior to baseline (continuous) and a factor score measuring consumption of an 'ethnic' dietary pattern in the year prior to baseline (continuous). HRs estimated using Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Table 12. Hazard ratios and 95% confidence intervals for breast cancer and vehicular traffic density (vehicle km traveled within 300m), by quartile categories, California Teachers Study cohort.

Population	Cases	Minimally adjusted[a] HR[c] (95% CI)	Fully adjusted[b] HR[c] (95% CI)
Total cohort			
Quartiles (N = 109,620)	4,201		
1		1.00 (ref)	1.00 (ref)
2		0.96 (0.88, 1.04)	0.96 (0.88, 1.05)
3		1.00 (0.92, 1.09)	1.00 (0.92, 1.09)
4		1.03 (0.95, 1.12)	1.02 (0.94, 1.11)
Non-movers			
Quartiles (N = 68,974)	2,918		
1		1.00 (ref)	1.00 (ref)
2		1.00 (0.90, 1.11)	1.00 (0.90, 1.11)
3		1.04 (0.94, 1.15)	1.04 (0.94, 1.15)
4		1.03 (0.93, 1.14)	1.03 (0.93, 1.14)
Never smokers			
Quartiles (N = 75,234)	2,544		
1		1.00 (ref)	1.00 (ref)
2		0.93 (0.83, 1.04)	0.93 (0.83, 1.04)
3		0.97 (0.87, 1.08)	0.97 (0.86, 1.08)
4		1.03 (0.92, 1.15)	1.02 (0.92, 1.14)
Non-movers and never smokers			
Quartiles (N = 46,736)	1,781		
1		1.00 (ref)	1.00 (ref)
2		1.01 (0.89, 1.16)	1.02 (0.89, 1.16)
3		1.04 (0.92, 1.19)	1.04 (0.91, 1.18)
4		1.03 (0.90, 1.17)	1.02 (0.90, 1.17)

[a] Adjusted for age and race/ethnicity.

[b] Adjusted for age, race, family history of breast cancer, age at menarche, pregnancy history, breast feeding history, physical activity, alcohol consumption, BMI, menopausal status/hormone therapy combined, smoking status, smoking pack-years, home environmental tobacco smoke exposure.

[c] HRs estimated using Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Table 13. Hazard ratios and 95% confidence intervals for breast cancer and industrial Cd emissions (kg/km within 5 km), by categories of exposure, California Teachers Study cohort.

Population	Cases	Minimally adjusted[a] HR[c] (95% CI)	Fully adjusted[b] HR[c] (95% CI)
Total cohort (N = 110,158)	4,223		
<75th percentile		1.00 (ref)	1.00 (ref)
75th-89th percentile		0.99 (0.91, 1.08)	0.99 (0.91, 1.08)
≥90th percentile		0.96 (0.86, 1.06)	0.96 (0.86, 1.06)
Non-movers (N = 68,975)	2,918		
<75th percentile		1.00 (ref)	1.00 (ref)
75th-89th percentile		1.01 (0.90, 1.12)	1.01 (0.91, 1.13)
≥90th percentile		0.97 (0.86, 1.10)	0.97 (0.86, 1.10)
Never smokers (N = 75,582)	2,558		
<75th percentile		1.00 (ref)	1.00 (ref)
75th-89th percentile		0.99 (0.89, 1.11)	0.99 (0.89, 1.11)
≥90th percentile		1.02 (0.89, 1.16)	1.02 (0.89, 1.16)
Non-movers and never smokers (N = 46,736)	1,781		
<75th percentile		1.00 (ref)	1.00 (ref)
75th-89th percentile		1.05 (0.91, 1.21)	1.05 (0.92, 1.21)
≥90th percentile		1.05 (0.90, 1.23)	1.05 (0.90, 1.23)

[a] Adjusted for age and race/ethnicity.

[b] Adjusted for age, race, family history of breast cancer, age at menarche, pregnancy history, breast feeding history, physical activity, alcohol consumption, BMI, menopausal status/hormone therapy combined, smoking status, smoking pack-years, home environmental tobacco smoke exposure.

[c] HRs estimated using Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Table 14. Hazard ratios and 95% confidence intervals for breast cancer and estimated outdoor Cd concentration, by categories of exposure and natural-logarithmic continuous exposure, California Teachers Study cohort.

Population	Cases	Minimally adjusted[a] HR[c] (95% CI)	Fully adjusted[b] HR[c] (95% CI)
Total cohort (N = 110,156)	4,223		
Categories			
<25th percentile		1.00 (ref)	1.00 (ref)
25th-49th percentile		1.08 (1.00, 1.18)	1.07 (0.98, 1.17)
50th-89th percentile		1.06 (0.98, 1.14)	1.04 (0.97, 1.13)
≥90th percentile		1.05 (0.94, 1.18)	1.06 (0.94, 1.19)
Log-continuous		1.03 (0.98, 1.09)	1.03 (0.98, 1.09)
Non-movers (N = 68,973)	2,918		
Categories			
<25th percentile		1.00 (ref)	1.00 (ref)
25th-49th percentile		1.14 (1.03, 1.26)	1.12 (1.01, 1.25)
50th-89th percentile		1.08 (0.98, 1.19)	1.07 (0.97, 1.18)
≥90th percentile		1.03 (0.90, 1.19)	1.04 (0.91, 1.20)
Log-continuous		1.01 (0.95, 1.08)	1.01 (0.95, 1.08)
Never smokers (N = 75,581)	2,558		
Categories			
<25th percentile		1.00 (ref)	1.00 (ref)
25th-49th percentile		1.11 (0.99, 1.23)	1.09 (0.98, 1.22)
50th-89th percentile		1.04 (0.94, 1.15)	1.02 (0.93, 1.13)
≥90th percentile		1.04 (0.90, 1.20)	1.04 (0.90, 1.20)
Log-continuous		1.01 (0.94, 1.08)	1.01 (0.94, 1.08)
Non-movers and never smokers (N = 46,735)	1,781		
Categories			
<25th percentile		1.00 (ref)	1.00 (ref)
25th-49th percentile		1.14 (1.00, 1.31)	1.13 (0.99, 1.29)
50th-89th percentile		1.05 (0.93, 1.18)	1.03 (0.91, 1.17)
≥90th percentile		1.09 (0.91, 1.29)	1.09 (0.92, 1.30)
Log-continuous		1.00 (0.92, 1.09)	1.00 (0.92, 1.08)

[a] Adjusted for age and race/ethnicity.

[b] Adjusted for age, race, family history of breast cancer, age at menarche, pregnancy history, breast feeding history, physical activity, alcohol consumption, BMI, menopausal status/hormone therapy combined, smoking status, smoking pack-years, home environmental tobacco smoke exposure.

[c] HRs estimated using Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Table 15. Hazard ratios and 95% confidence intervals for ER-positive and ER-negative breast cancer and estimated outdoor Cd concentration, by categories of exposure and natural-logarithmic continuous exposure, California Teachers Study cohort.

	ER-positive			ER-negative		
Population	N	Cases	HR[a] (95% CI)	N	Cases	HR[a] (95% CI)
Total cohort	109,050	3,117		106,478	545	
Categories						
<25th percentile			1.00 (ref)			1.00 (ref)
25th-49th percentile			1.15 (1.04, 1.27)			0.90 (0.70, 1.15)
50th-89th percentile			1.08 (0.98, 1.18)			1.10 (0.89, 1.36)
≥90th percentile			1.07 (0.94, 1.23)			1.21 (0.89, 1.63)
Log-continuous			1.03 (0.97, 1.10)			1.14 (0.98, 1.31)
Non-movers	68,235	2,180		66,413	358	
Categories						
<25th percentile			1.00 (ref)			1.00 (ref)
25th-49th percentile			1.21 (1.08, 1.37)			1.02 (0.74, 1.39)
50th-89th percentile			1.10 (0.99, 1.23)			1.25 (0.95, 1.64)
≥90th percentile			1.06 (0.90, 1.25)			1.30 (0.89, 1.91)
Log-continuous			1.01 (0.94, 1.09)			1.17 (0.98, 1.39)
Never smokers	74,892	1,869		73,366	343	
Categories						
<25th percentile			1.00 (ref)			1.00 (ref)
25th-49th percentile			1.18 (1.04, 1.34)			1.01 (0.74, 1.37)
50th-89th percentile			1.05 (0.93, 1.18)			1.11 (0.84, 1.47)
≥90th percentile			1.08 (0.91, 1.28)			1.26 (0.86, 1.84)
Log-continuous			1.00 (0.93, 1.09)			1.14 (0.95, 1.37)
Non-movers and never smokers	46,267	1,313		45,182	228	
Categories						
<25th percentile			1.00 (ref)			1.00 (ref)
25th-49th percentile			1.22 (1.05, 1.43)			1.17 (0.79, 1.74)
50th-89th percentile			1.05 (0.91, 1.21)			1.30 (0.92, 1.85)

≥90th percentile	1.11 (0.91, 1.36)	1.64 (1.04, 2.59)
Log-continuous	0.99 (0.89, 1.08)	1.24 (1.00, 1.53)

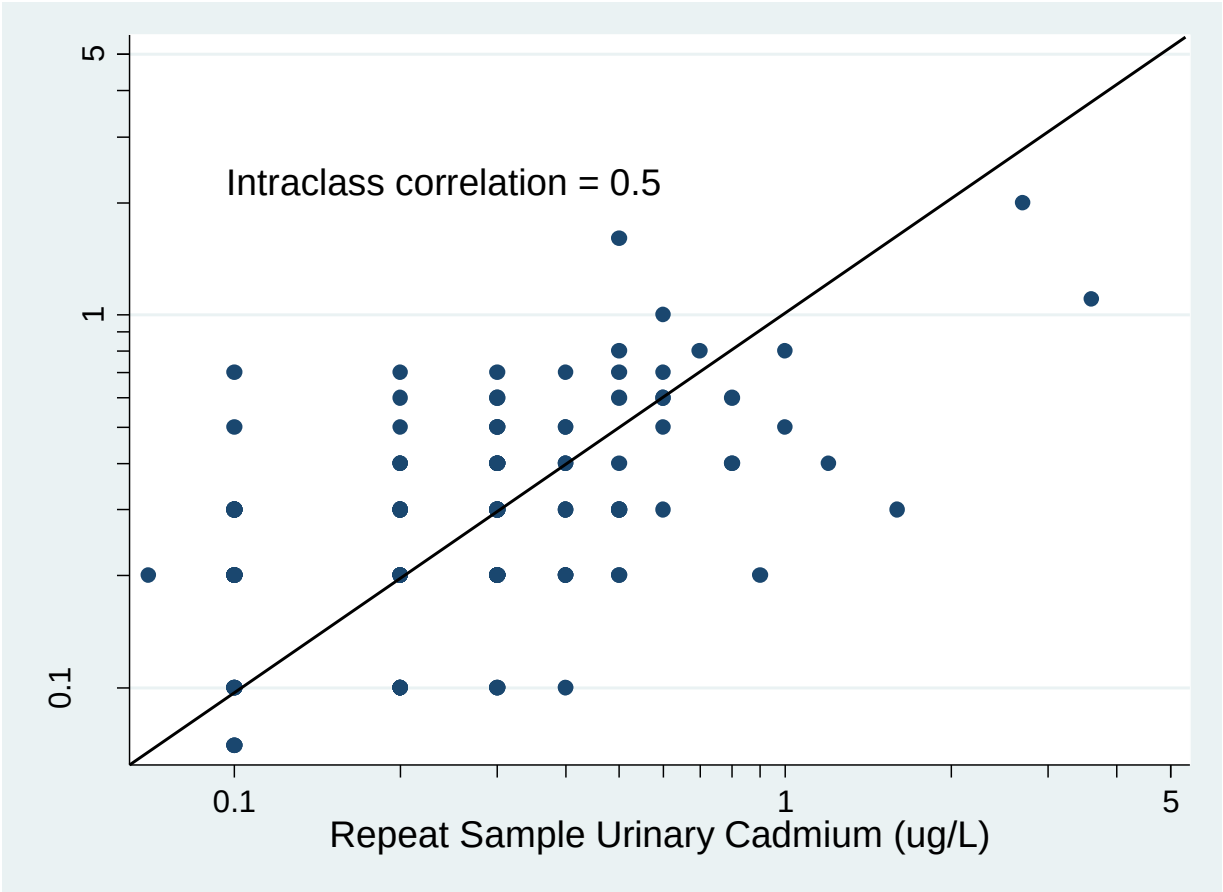
[a] Adjusted for age, race, family history of breast cancer, age at menarche, pregnancy history, breast feeding history, physical activity, alcohol consumption, BMI, menopausal status/hormone therapy combined, smoking status, smoking pack-years, home environmental tobacco smoke exposure. HRs estimated using Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Table 16. Hazard ratios and 95% confidence intervals for ER-positive and ER-negative breast cancer and traffic density (vehicle km traveled within 300m), by quartile categories, California Teachers Study cohort.

		ER-positive		ER-negative	
Population	N	Cases	HR[a] (95% CI)	Cases	HR[a] (95% CI)
Total cohort	105,419	3,105		541	
Quartiles					
1			1.00 (ref)		1.00 (ref)
2			0.98 (0.88, 1.08)		1.09 (0.85, 1.38)
3			1.03 (0.94, 1.14)		1.12 (0.88, 1.43)
4			1.07 (0.96, 1.18)		1.15 (0.90, 1.46)
Non-movers	66,056	2,180		358	
Quartiles					
1			1.00 (ref)		1.00 (ref)
2			1.00 (0.88, 1.12)		1.28 (0.94, 1.73)
3			1.06 (0.94, 1.19)		1.24 (0.92, 1.68)
4			1.05 (0.94, 1.18)		1.28 (0.95, 1.72)
Never smokers	72,690	1,861		341	
Quartiles					
1			1.00 (ref)		1.00 (ref)
2			0.96 (0.85, 1.10)		1.20 (0.88, 1.64)
3			1.01 (0.88, 1.15)		1.18 (0.86, 1.61)
4			1.09 (0.96, 1.24)		1.30 (0.96, 1.77)
Non-movers and never smokers	44,955	1,313		228	
Quartiles					
1			1.00 (ref)		1.00 (ref)
2			1.03 (0.88, 1.21)		1.39 (0.95, 2.03)
3			1.07 (0.92, 1.25)		1.30 (0.89, 1.91)
4			1.06 (0.91, 1.24)		1.42 (0.97, 2.07)

[a] Adjusted for age, race, family history of breast cancer, age at menarche, pregnancy history, breast feeding history, physical activity, alcohol consumption, BMI, menopausal status/hormone therapy combined, smoking status, smoking pack-years, home environmental tobacco smoke exposure. HRs estimated using Cox regression with age (in days) as the time-scale and stratified by age (in years) at baseline.

Figure 1. Intraclass correlation for repeated measurements of cadmium in urine (CTS exposure validation sub-study, n=141).



APPENDIX 1

Era of Hope 2011 Conference, Poster Abstract, "Urinary Cadmium Concentrations among Female Teachers from Northern California"

Urinary Cadmium Concentrations among Female Teachers from Northern California

Authors: Robert Gunier, Rudy Rull, Andrew Hertz, Alison Canchola, Pamela Horn-Ross, Peggy Reynolds

Background: Cadmium is a toxic metal associated with kidney disease and increased mortality. It has been classified as a probable human carcinogen, demonstrated to have estrogenic properties, and associated with breast cancer in previous case-control studies. Exposure to cadmium occurs from smoking, diet and inhalation of air polluted from combustion, mining, and manufacturing. Excretion of cadmium in urine is widely considered a biomarker of lifetime exposure. Urinary cadmium concentration has been associated with age, smoking status, body surface area, parity, and household income in previous studies. Our objectives were to identify predictors of urinary cadmium concentrations and determine the within-person correlation among repeat samples.
Methods: We collected a 24-hour urine sample from 298 women enrolled in the California Teachers Study in 2000 and a second 24-hour sample from 141 participants approximately three, six, or nine months later. Urinary cadmium concentrations (µg/L) were determined by inductively-coupled plasma/mass spectrometry. Age, body mass index, smoking status, passive smoking, dietary intake, alcohol consumption, parity, and several reproductive factors were obtained by interview. Environmental cadmium exposure from vehicular traffic and from industrial and commercial emission sources around the address of residence as well as modeled outdoor air concentrations were estimated using a geographic information system. Dietary cadmium intake was assessed by linking data from a food-frequency questionnaire with the Total Diet Study database. We used mixed-effects models to estimate the within-person correlation between repeat measurements and identify predictors of urinary cadmium levels.
Results: The arithmetic mean cadmium concentration was 0.3 micrograms per liter (µg/L) (standard deviation = 0.2 µg/L) and the range was 0.1 to 2.0 µg/L. The intra-class correlation among repeat samples from the same individual was 0.5. Urinary cadmium concentration increased with age, creatinine concentration, lifetime pack-years of smoking, lifetime intensity of passive smoking among non-smokers, and decreased with greater alcohol consumption and number of previous pregnancies. These factors explained 44% of the variability in urinary cadmium concentrations. However, cadmium exposures from environmental or dietary sources did not appear to be associated with urinary concentrations.
Conclusion: These results suggest that a single measurement of urinary cadmium concentration does not accurately assess lifetime exposure. Although our estimates of environmental and dietary exposure were not associated with urinary cadmium levels, we will evaluate whether these exposures are associated with breast cancer risk. If increased risks are observed with estimated cadmium exposure, our results could serve as the impetus for future regulatory actions to mitigate cadmium exposure and ultimately reduce the burden of breast cancer in women.

APPENDIX 2

Scientific Abstract, "Cadmium, Age at Menarche, and Early Pubertal Development in Girls" (California Breast Cancer Research Program Award #17IB-0016)

Background and overall topic: Women who experience their first menstrual period (i.e., menarche) before the age of 12 years have an increased risk of breast cancer. It has been estimated that each one-year decrease in age at menarche is associated with a 5-10% elevation in risk of this disease. This association is consistent with the hypothesis that the earlier establishment of ovulatory cycles which in turn increases the the period during which breast cells are most mitotically active and susceptible to tumorigenic somatic events. Early menarche has also been associated with higher cumulative exposure to estrogens.

Over the past two decades the average age at menarche has been declining in the US and Europe. While the causes of early menarche and pubertal development are largely unknown, emerging evidence from animal and in vitro studies suggest that increasing exposures to estrogenic environmental chemicals may be contributing to this trend. Cadmium (Cd), a trace metal released into air and soil as a byproduct of industrial processes, is perhaps the most potent of these estrogenic contaminants. Previous epidemiologic studies have observed an association between a higher body burden of Cd and breast cancer risk. While the major sources of non-occupational exposure to Cd in adults include cigarette smoke, diet, and inhalation of ambient air contaminated by industrial processes and combustion of fossil fuels, recent discoveries of Cd in children's toys and jewelry have led to public concern about potential childhood exposure from ingestion and hand-to-mouth activity. However, it is not known whether this estrogenic metal may contribute to early menarche and puberty in girls.

Hypothesis/questions addressed: The primary hypothesis of this proposal is that urinary Cd concentration, a marker of lifetime body burden, is associated with an earlier age at menarche and early onset of pubertal development.

Objectives/aims: Our specific aims are as follows:

1. Determine the urinary concentrations of Cd, a measure of lifetime exposure and body burden, in a cohort of girls and whether concentrations differ by age, race/ethnicity, and among Chinese girls, nativity and generational status.
2. Evaluate whether urinary Cd concentration is associated with early age at menarche.
3. Evaluate whether urinary Cd concentration is associated with earlier estrogen-based or androgen-based pubertal development.

Methods and approaches: This proposed study will utilize existing data and urine specimens from the GRowth and LifeStyle Study (GRLS), a prospective cohort study of girls. A total of 214 girls, aged 10-13 years at baseline and primarily non-Hispanic White or Chinese, provided overnight urine specimens at baseline that will be used to measure urinary Cd concentrations, completed a baseline interview, provided a self-assessment of Tanner stage based on standard pictorial depictions and verbal descriptions of breast development and public hair growth, and had their height and weight measured. A total of 87 girls had their first menstrual period prior to baseline, while 134 girls were pre-menarcheal at baseline and followed for up to two years using monthly questionnaires to ascertain the onset of menarche and an annual interview that included self-assessed Tanner stage and the collection of an additional overnight urine specimen. We will evaluate the hypothesis that Cd body burden is associated with early menarche and pubertal development using regression-based longitudinal and cross-sectional approaches.

Impact on breast cancer: Early-life exposure to this estrogenic metal may contribute to earlier pubertal development and attainment of menarche and thus also play a role in the etiology of breast cancer. As Cd exposures are potentially modifiable, this proposed study offers tremendous potential to contribute to our knowledge about the etiology of early menarche, a known risk factor for breast cancer.

Advocacy involvement and sensitivity to advocacy concerns: This project has high potential for meaningful translation into the reduction of children's exposures to this estrogenic metal. If this study finds an association between early pubertal development and Cd exposure, it could provide a major impetus for further regulatory actions to reduce both the use of Cd in industrial processes and thus exposure in children and adults. To ensure our results are translated into actions aimed at mitigating the burden of exposure, we will disseminate our results to the scientific and lay communities, as well as to policy makers, in the form of a scientific manuscript and lay-friendly fact sheet. Breast cancer and environmental advocacy organizations will play a critical role in the translation of findings from our study into meaningful and measurable interventions.